Citation:

He Feng J, Marciniak M, Visagie E, Markandu ND, Anand V, Dalton RN, MacGregor GA. Effect of Modest Salt Reduction on Blood Pressure, Urinary Albumin and Pulse Wave Velocity in White, Black and Asian Mild Hypertensives. *Hypertension* Sep 2009.

PubMed ID: 19620514

Study Design:

Randomized, double-blind, crossover trial

Class:

A - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

POSITIVE: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

- To determine the effects of a modest reduction in salt intake, as recommended, on blood pressure (BP) in three ethnic groups whites, blacks and Asians) with untreated mildly raised BP
- To determine the effects of a modest reduction in salt intake on 24-hour urinary albumin excretion and pulse wave velocity.

Inclusion Criteria:

- Age 30 to 75 years
- Sitting systolic BP (SBP) 140 to 170mmHg or diastolic BP (DBP) 90 to 105mmHg
- No previous treatment for raised BP.

Exclusion Criteria:

- Any secondary cause of hypertension
- Impaired renal function with plasma creatinine >150µmol/L
- Previous stroke
- Ischemic heart disease
- Heart failure
- Diabetes mellitus
- Malignancy
- Liver disease
- Women who were pregnant, breastfeeding or on oral contraceptive pills.

Description of Study Protocol:

Recruitment

- Participants were recruited from the Blood Pressure Unit outpatient clinic and from general practices in South London

- The classification of ethnic groups was based on participants' self-identified ethnicity, and further assessed by research nurses according to skin color and participants' and their parents' country of origin.

Design

- Randomized, double-blind crossover trial
- Patients remained on the reduced salt diet introduced within the first two weeks of the study, but were randomized to either slow sodium or placebo
- Randomization was stratified according to ethnic group using computer-generated random number, carried out by an independent company-Healthspan Group Ltd, who supplied slow sodium and slow sodium matching placebo tablets but had no involvement in the conduct of the trial
- Participants were allocated in random order to either slow sodium or placebo for six weeks
- They then crossed over to take the opposite tablets for six further weeks.

Blinding

- Slow sodium matching placebo tablets were provided to maintain blinding of participants
- All participants and research staff were unaware of treatment allocation.

Intervention

- All groups:
    - Participants were given detailed advice by specially trained nurses on how to reduce their salt intake, with an aim of achieving an intake of approximately five grams per day (85mmol per day)
    - They were advised not to add salt at the table or during cooking and avoid foods that contained large amount of salt
    - Nurses went through with participants on what foods they usually ate and identified items with high salt content and advised them to use low salt alternatives
    - In appropriate cases, the spouse or whoever cooked in the household was also seen
    - Advice was reinforced at each visit for the whole duration of the study
    - Salt-free bread was provided for those who had no easy access to it.
- Intervention group:
    - Nine slow sodium tablets (10mmol sodium per tablet) daily for six weeks
- Control group:
    - Nine placebo tablets daily for six weeks.

Statistical Analysis

- By means of sample size calculation, we estimated that 70 participants in each ethnic group (allowing 5% drop-out rate) were needed to detect a change of 4mmHg in SBP between slow sodium and placebo, with a power of 90% and alpha=0.05, given a standard deviation (SD) of 10
- This calculation was based on a very conservative estimate of a difference of 4mmHg in SBP between the two treatment periods
- Paired Student T test was used to compare the difference between slow sodium and placebo for normally distributed variables, and Wilcoxon signed ranks test was used for variables that were not normally distributed (i.e., plasma renin activity, 24-hour urinary albumin, urinary albumin/creatinine ratio)
- A two-tailed probability value of <0.05 was regarded as statistically significant
- All statistical analyses were performed using SPSS.

Data Collection Summary:

Timing of Measurements

- All measurements were taken at baseline while on individuals' usual diet
- All other measurements were performed at the end of each six-week period.

Dependent Variables

- Blood pressure was measured by a validated automatic digital BP monitor in sitting position after five- to 10-minute rest and in the same arm throughout the study. Three readings were taken at one- to two-minute intervals, and the mean of last two readings was used
- 24-hour ambulatory BP monitoring was performed using SpaceLabs 90207 devices
- Blood samples were taken for measurements of routine biochemistry, plasma rennin activity and aldosterone
- Two consecutive 24-hour urines were collected for measurements of urinary sodium, potassium, creatinine, calcium and albumin. Participants were carefully instructed on how to accurately collect 24-hour urine by research nurses. The mean of two urinary measurements was used in the analysis. Urinary albumin was measured by laser immunonephelometry. Urine samples with measured concentrations <2.1mg/L were re-analyzed using a high sensitivity ELISA
- Carotid-femoral pulse wave velocity was measured non-invasively using an automatic device. Two pressure waveforms were recorded simultaneously with pressure-sensitive transducers which were placed on the skin at two sites, the common carotid artery and the femoral arther. The pressure waveforms were digitized, and calculation of the time delay between the two pressure upstrokes was initiated automatically. Measurement was repeated over 10 cardiac cycles and the mean was used.

Independent Variables

Sodium intake represented by 24-hour urinary sodium excretion.

Control Variables

None.

Description of Actual Data Sample:

- *Initial N*: 187 individuals entered the study
- *Attrition (final N):* Before randomization, two blacks withdrew, leaving 185 participants who entered the randomized crossover trials. In total, 169 participants completed the trial and 16 (six whites, four blacks and six Asians) withdrew. Results reported are based on the 169 participants who completed the study (113 males; 56 females)
- *Age:* 37-64 years
- *Ethnicity:* White, Black and Asian
- *Location:* Clinics in South London.

Summary of Results:

Key Findings (all participants)

- At baseline, the mean 24-hour urinary sodium was 131±50mmol which is equivalent to 7.7g of salt
- During the randomized crossover phase, the mean 24-hour urinary sodium was 165±58 mmol (9.7g salt) on slow sodium and 110±49mmol (6.5g salt) on placebo. There was therefore a reduction of 55mmol (3.2g salt) from slow sodium to placebo
- With this reduction in salt intake, BP fell from 146±13/91±8mmHg on slow sodium to 141±12/88±9mmHg on placebo (i.e. an average fall of 4.8mmHg [P<0.001] in SBP and 2.2mmHg

[P<0.001] in DBP)
- Pulse pressure also fell significantly
- There were significant falls in mean 24-hour, daytime and nighttime BP
- The median 24-hour urinary albumin was 10.2 (interquartile range, IQR: 6.8 to 18.9) on slow sodium, and 9.1mg (6.6 to 14.0) on placebo. There was, therefore, an 11% reduction (P<0.001) from slow sodium to placebo
- Furthermore, there was a significant reduction in urinary albumin/creatinine ratio
- From slow sodium to placebo, there was a significant decrease in pulse wave velocity
- Both 24-hour urinary calcium and calcium/creatinine ratio were reduced significantly
- There was also a small but significant reduction in body weight, an increase in plasma rennin activity and aldosterone, and a small but significant increase in plasma creatinine.

Table: Changes in Variables From Slow Sodium to Placebo in All Participants

Variable	Slow Sodium	Placebo	Difference (95% CI)	P-Value
Office BP and pulse rate				
SBP, mmHg	146±13	141±12	-4.8 (-6.4, -3.2)	<0.001
DBP, mmHg	91±8	88±9	-2.2 (-3.1, -1.4)	<0.001
Pulse pressure, mmHg	55±11	53±10	-2.6 (-3.8, -1.4)	<0.001
Pulse rate, bpm	66±11	67±10	0.8 (-0.3, 1.9)	0.172
Ambulatory BP, mmHg				
24-hour SBP	141±10	137±11	-4.1 (-5.2, -3.0)	<0.001
24-hour DBP	86±9	84±9	-1.9 (-2.6, -1.1)	<0.001
Day SBP	147±10	143±11	-4.7 (-5.9, -3.4)	<0.001
Day DBP	92±9	90±9	-2.2 (-3.1, -1.3)	<0.001
Night SBP	133±11	130±12	-3.5 (-4.9, -1.3)	<0.001
Night DBP	80±9	78±10	-1.7 (-2.7, -0.7)	0.001
Urinary measurements				
Volume, ml per 24 hours	1,730±697	1,736±716	6 (-68,80)	0.872
Sodium, mmol per 24 hours	165±58	110±49	-55 (-64,-46)	<0.001
Body weight, kg	85.5±17.4	85.2±17.5	-0.3 (-0.5, -0.04)	0.021
Pulse wave velocity, ms	11.5±2.3	11.1±1.9	-0.3 (-0.6, -0.1)	0.004

Plasma measurements: All values are expressed as mean ±SD unless marked with * where values are median (IQR)

Results by ethnic group:

- From slow sodium to placebo, salt intake as calculated from 24-hour urinary sodium was reduced by 3.5g per day in whites, 2.7g per day in blacks and 4.0g per day in Asians. With these reductions in salt intake, there were significant falls in BP in all three ethnic groups
- BP fell by 4.6/2.2, 4.8/2.2 and 5.4/2.2 mmHg in whites, blacks and Asians, respectively
- Pulse pressure also fell significantly in all groups
- Daytime BP showed a significant fall in all groups, and nighttime BP fell significantly in whites and

blacks, but not in Asians
- With salt reduction, 24-hour urinary albumin was reduced by 9% in whites (P<0.05), 14% in blacks (P=0.057), and 14% in Asians (P<0.05)
- There was a significant decrease in urinary albumin/creatinine ratio in all three groups
- From slow sodium to placebo, pulse wave velocity was decreased significantly in blacks but not whites and Asians
- There were significant reductions in both 24-hour urinary calcium and calcium/creatinine ratio in all three groups
- Plasma rennin activity and aldosterone showed significant increases in whites, but in blacks and Asians there was NS change in either parameter.

Table: Changes in Variables From Slow Sodium to Placebo by Ethnic Group

	Whites		Blacks		Asians	
Variable	**Slow sodium**	**Placebo**	**Slow sodium**	**Placebo**	**Slow sodium**	**Placebo**
Office BP and pulse rate						
SBP, mmHg	145±12	141±12[b]	149±13	144±12[c]	140±12	134±13[b]
DBP, mmHg	90±7	88±8[b]	91±9	89±9[b]	91±8	89±9[a]
Pulse pressure, mmHg	55±10	53±11[a]	58±11	55±10[a]	49±7	46±8[a]
Pulse rate, bpm	65±11	66±10[a]	68±10	67±10	67±11	69±12
Ambulatory BP, mmHg						
24-hour SDP	138±9	134±10[c]	145±9	140±10[c]	137±12	135±12
24-hour DBP	85±8	83±8[b]	88±9	86±10[b]	87±9	85±8
Day SBP	146±10	141±10[c]	150±10	145±11[c]	144±11	140±13[a]
Day DBP	91±9	89±9[a]	93±10	90±10[b]	93±9	90±9[a]
Night SBP	129±10	126±11[c]	138±10	134±12[c]	130±12	129±13
Night DBP	78±8	75±8[a]	83±9	81±10[a]	80±8	80±10
Urinary measurements						
Volume, ml per 24 hours	1,919±792	1,950±783	1,552±567	1,537±629	1,689±630	1,686±602
Sodium, mmol per 24 hours	163±65	104±54[c]	162±28	116±44[c]	176±64	108±49[c]
Albumin, mg per 24 hours*	9.6 (6.2, 16.1)	8.7 (6.5, 13.1)[a]	11.3 (6.4, 21.1)	9.7 (6.7, 18.2)	9.5 (7.0, 16.0)	8.2 (6.6, 13.2)
Albumin/creatinine ratio, mg/mmol*	0.72 (0.45, 1.31)	0.62 (0.41, 0.98)[b]	0.89 (0.49, 1.70)	0.68 (0.42, 1.45)[b]	0.86 (0.57, 1.54)	0.75 (0.57, 1.04)
Pulse wave velocity, ms	11.3±2.6	11.1±1.9	11.7±2.0	11.2±1.8[c]	11.3±2.2	11.2±2.2
Plasma measurements						
Sodium, mmol/L	139.5±1.74	139.3±2.1	139±2.0	139.9±2.3[d]	139.9±2.4	138.9±1.6[a]

Renin activity, ng/ml/hr*	0.35 (0.12, 0.72)	0.55 (0.25, 0.95)[c]	0.10 (0.10, 0.11)	0.10 (0.10, 0.17)	0.12 (0.10, 0.62)	0.20 (0.11, 0.63)
Aldosterone, pmol/L	414±174	486±186[c]	303±142	332±161	390±206	423±172

All values are expressed as mean±SD unless marked with * where values are median (IQR). ap<0.05, bp<0.01, cp<0.001, dp=0.050, ep=0.057 compared to slow sodium period.

Author Conclusion:

- This study is the largest double-blind trial of modest salt reduction which also involves a large number of black and Asian participants
- The study demonstrates that a modest reduction in salt intake, as currently recommended, causes significant and important falls in BP in all three ethnic groups of individuals with mildly raised BP
- Longer term reduction in salt intake reduces urinary albumin excretion in white, black and Asian hypertensive individuals
- In blacks, a modest reduction in salt intake reduces carotid-femoral pulse wave velocity, suggesting an improvement in large elastic artery compliance
- Modest reduction in salt intake has other beneficial effects (i.e., reducing urinary albumin excretion, improving large elastic artery compliance and decreasing urinary calcium excretion)
- This study provides further support for the current recommendations to reduce salt intake to less than 6 g per day in adults.

Reviewer Comments:

- *The reasons for withdrawals were not described*
- *While the patients included in the study had mildly elevated blood pressure, the methods did not describe the potential use of anti-hypertensive agents if the patients developed hypertension while participating in the study. It is possible that over the course of the study, a patient's blood pressure may have worsened and subsequently been treated with an anti-hypertensive agent, confounding the blood pressure results of the trial*
- *Intention to treat analysis was not performed and results were only presented on those who completed the studies*
- *The authors did not discuss any limitations of the study.*

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions		
1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	Yes
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes

4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	Yes

Validity Questions

1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
3.	**Were study groups comparable?**	Yes
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	Yes
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	Yes
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	Yes
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	N/A
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	Yes
4.1.	Were follow-up methods described and the same for all groups?	Yes
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	Yes

4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	???
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	Yes
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	Yes
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	N/A
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	Yes
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	N/A
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	Yes
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	???
6.6.	Were extra or unplanned treatments described?	???
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	Yes
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes

7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	???
7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	N/A
8.6.	Was clinical significance as well as statistical significance reported?	Yes
8.7.	If negative findings, was a power calculation reported to address type 2 error?	N/A
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**	No
9.1.	Is there a discussion of findings?	Yes
9.2.	Are biases and study limitations identified and discussed?	No
10.	**Is bias due to study's funding or sponsorship unlikely?**	Yes
10.1.	Were sources of funding and investigators' affiliations described?	Yes
10.2.	Was the study free from apparent conflict of interest?	Yes